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| 09/685,696 | 10/09/2000 | Tongtong Wang | 210121.455C13 | 3927 |

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| EXAMINER |
|---|
| CHEN, SHIN LIN |

| ART UNIT | PAPER NUMBER |
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| 1632 | 15 |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/685,696 | Applicant(s) WANG ET AL. | |
|---|---|---|---|
| | Examiner Shin-Lin Chen | Art Unit 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 July 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *4-11,16,23-30 and 32-70* is/are pending in the application.

4a) Of the above claim(s) *4-11,16,23-30 and 32-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *61-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10,14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

Applicants' amendment filed 7-3-02 has been entered. Claims 1-3, 12-15, 17-22 and 31 have been canceled. Claims 61-70 have been added. Claims 4-11, 16, 23-30 and 32-70 are pending and claims 61-70 are under consideration.

### *Claim Rejections - 35 USC § 112*

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 61-70 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants' amendment filed 7-3-02 necessitates this new ground of rejection.

The claimed invention is drawn to an immunogenic composition comprising an immunostimulant and a polypeptide comprising SEQ ID No. 176 or a portion thereof, or a polypeptide comprising an amino acid sequence having at least 75% or 90% identity to the sequence of SEQ ID No. 176, and the use of said immunogenic composition to induce an immune response in a patient. The specification states that the amino acid sequence of SEQ ID

No. 176 is encoded by the polynucleotide sequence of SEQ ID NO. 175, which is a full-length cDNA sequence of L523S clone.

The claims encompass a genus of various structural variants of polypeptide sequence of SEQ ID No. 176. A polypeptide comprising an amino acid sequence having at least 75% or 90% identity to the sequence of SEQ ID No. 176 encompass adding unknown and unidentified amino acid sequence to 5' and/or 3' or within the sequence of SEQ ID No. 176 and includes numerous unknown and unidentified polypeptides that differ dramatically from the sequence of SEQ ID No. 176.

The scope of the claim includes a genus of numerous structural variants of SEQ ID No. 176, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification fails to provide sufficient disclosure of the structural feature within protein sequence of SEQ ID No. 176 that contributes to the production of antibody specific to SEQ ID No. 176 and said antibody could be used for the detection of lung cancer. The specification also fails to provide sufficient disclosure of the structural feature, such as an antigenic determinant, of SEQ ID No. 176 which can induce immune response in a patient. Therefore, structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe common attributes or characteristics that identify

members of the genus, and because the genus is highly variant, the disclosure of SEQ ID No. 176 is insufficient to describe the genus.

This limited information is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of numerous variants of SEQ ID No. 176 as claimed in the present invention. Thus it is concluded that the written description requirement is not satisfied for the genus.

Applicants argue that the specification discloses a single identifying characteristic common to the claimed polynucleotides, i.e. the ability to detect lung cancer or to stimulate T cells (amendment, p. 8-9). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 112 first paragraph written description rejection.

3. Claims 61-64 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 61-64 read on using the claimed polypeptide for the detection of lung cancer. The specification fails to provide sufficient disclosure that any polypeptide can be used for detection of lung cancer. Thus, the phrase "wherein said polypeptide can be used for detection of lung cancer" in claim 61 line 9 is considered new matter.

***Claim Rejections - 35 USC § 112***

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 61-64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide comprising the amino acid sequence of SEQ ID No. 176 for production of antibody that is used for the detection of lung cancer, does not reasonably provide enablement for a polypeptide comprising an amino acid sequence having at least 75% or 90% identity to the sequence of SEQ ID No. 176, wherein said polypeptide can be used for detection of lung cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicants' amendment filed 7-3-02 necessitates this new ground of rejection.

Claims 61-64 are directed to an immunogenic composition comprising an immunostimulant and a polypeptide comprising SEQ ID No. 176 or a portion thereof, or a polypeptide comprising an amino acid sequence having at least 75% or 90% identity to the sequence of SEQ ID No. 176, and the use of said immunogenic composition to detect lung cancer. The specification only discloses over-expression of SEQ ID No. 175 and SEQ ID No. 176 in lung tumor tissues as compared to normal lung tissues.

The claims encompass a genus of various structural variants of polypeptide sequence of SEQ ID No. 176. A polypeptide comprising an amino acid sequence having at least 75% or 90%

identity to the sequence of SEQ ID No. 176 encompass adding unknown and unidentified amino acid sequence to 5' and/or 3' or within the sequence of SEQ ID No. 176 and includes numerous unknown and unidentified polypeptides that differ dramatically from the sequence of SEQ ID No. 176. The specification fails to provide sufficient disclosure of the structural feature, such as antigenic determinant, within protein sequence of SEQ ID No. 176 that contributes to the production of antibody specific to SEQ ID No. 176.

It was well known in the art that the size of a polypeptide, the three dimensional conformation or stereochemical shape of the polypeptide, the structural stability of the polypeptide, and antigenic determinant or epitopes of the polypeptide are important factors for antigenicity of a polypeptide. A polypeptide comprising an amino acid sequence having at least 75% or 90% identity to the sequence of SEQ ID No. 176 would encompass substitution, deletion, or addition of amino acid residues within SEQ ID No. 176 and lead to various different polypeptide sequences. The alteration of amino acid sequence of a polypeptide can change its stereochemical shape or three dimensional conformation or its antigenic determinant region, and such alteration can change the ability of the polypeptide in producing antibody specific to SEQ ID No. 176. It would be unpredictable for one skilled in the art at the time of the invention to determine which amino acid residue can be substituted, deleted, or added to SEQ ID No. 176 and the resulting polypeptide still produce antibody specific to SEQ ID No. 176 for the detection of lung cancer in a patient. Thus, one skilled in the art at the time of the invention would not know how to use the claimed polypeptides.

In addition, the claimed polypeptides encompass polypeptide having altered antigenic determinant region of SEQ ID No. 176 and said polypeptide would produce antibody that is specific to said polypeptide but not to SEQ ID No. 176. The specification fails to provide adequate guidance and evidence for how to use antibody specific to polypeptide having altered antigenic determinant region of SEQ ID No. 176 to measure the expression level of SEQ ID No. 176 in a biological sample or to detect the presence of lung cancer in a patient. One skilled in the art would not know how to use the claimed polypeptides to produce antibody specific to SEQ ID No. 176 for the detection of lung cancer.

Further, Claims 61-64 read on using a polypeptide to detect lung cancer. The specification fails to provide adequate guidance and evidence for how to use a polypeptide to detect lung cancer in a biological sample. A polypeptide can be used to raise antibody specific to said polypeptide and said antibody can be used for diagnostic purpose. However, there is no evidence of record that the claimed polypeptides can be used to detect lung cancer in a biological sample and the specification fail to provide an enabling disclosure for using a polypeptide to detect lung cancer. Therefore, one skilled in the art at the time of the invention would not know how to use the claimed polypeptides to detect lung cancer.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the

breadth of the claims, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

6. Claims 65-70 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 65-70 are directed to an immunogenic composition comprising an immunostimulant and a polypeptide comprising SEQ ID No. 176 or a portion thereof, or a polypeptide comprising an amino acid sequence having at least 75% or 90% identity to the sequence of SEQ ID No. 176, and the use of said immunogenic composition to induce immune response in a patient or stimulate T cells that are specific for SEQ ID No. 176.

Since the polypeptide sequence of SEQ ID No. 176 is overexpressed in lung cancer as compared to normal lung tissues, it is considered a lung tumor protein. Claims 65-70 read on using the claimed immunogenic composition to stimulate T cells or an immune response in a patient so as to provide a therapeutic effect, such as inhibition of tumor growth or elimination of tumor cells, in said patient. The specification fails to provide adequate guidance and evidence that the immunogenic composition comprising the claimed polypeptides can stimulate any T cells or an immune response in a patient so as to provide a therapeutic effect, such as inhibition of tumor growth or elimination of tumor cells, in said patient.

As discussed above, the size of a polypeptide, the three dimensional conformation or stereochemical shape of the polypeptide, the structural stability of the polypeptide, and antigenic determinant or epitopes of the polypeptide are important factors for antigenicity of a polypeptide. A polypeptide comprising an amino acid sequence having at least 75% or 90% identity to the sequence of SEQ ID No. 176 would encompass substitution, deletion, or addition of amino acid residues within SEQ ID No. 176 and lead to various different polypeptide sequences. The alteration of amino acid sequence of a polypeptide can change its stereochemical shape or three dimensional conformation or its antigenic determinant region, and such alteration can change the ability of the polypeptide in producing antibody specific to SEQ ID No. 176 or a particular immune response specific to various target tumor cells including lung tumor cells, breast tumor cells, prostate tumor cells etc., in a patient. It would be unpredictable for one skilled in the art at the time of the invention to determine which amino acid residue can be substituted, deleted, or added to SEQ ID No. 176 and the resulting polypeptide still produce antibody specific to SEQ ID No. 176 or induction of immune response specific to various target tumor cells in a patient. Thus, one skilled in the art at the time of the invention would not know how to use the claimed polypeptides for the claimed invention.

In addition, it was known in the field of immunology that antigenic tumor keep growing in spite of demonstrable antitumor T-cell immune response. Radoja (2000, Molecular Medicine, 6(6): 465-479) discloses that there are several different biochemical defects in T lymphocytes that infiltrate cancers and tumors or host cells recruited to the tumor site actively down-regulate

antitumor T-cell immune response, thus, permits tumor escape from immune-mediated killing (e.g. abstract, introduction). Radoja hypothesizes that immunogenic tumors escape T cell killing because tumor infiltrating lymphocytes (TIL) receive an abortive apoptotic signal that inactivates TCR-mediated signal transduction and renders them anergic (e.g. p. 470, right column). Thus, it is evident that at the time of the invention, the skilled artisan in the relevant art, while acknowledging the significant potential of immunotherapy for cancer, still recognized that such therapy was neither routine nor accepted, and awaited significant development and guidance for its practice. Therefore, one skilled in the art at the time of the invention would require undue experimentation to practice over the scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Applicants argue that the biological function of SEQ ID No. 176 or polypeptide that is at least 75% or 90% identical to SEQ ID No. 176 is irrelevant to its use in detection of lung cancer or stimulation of T cell response, and it is routine experimentation to whether the claimed polypeptides can be used to detect lung cancer or to stimulate T cell response (amendment, p. 7). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 112 first paragraph enablement rejection.

*Claim Rejections - 35 USC § 103*

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 61, 62, 65-67 and 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carney (US Patent No. 6,200,764) in view of Mueller-Pillasch et al., 1997 (Oncogene, Vol. 14, p. 2729-2733).

Claims 61, 62, 65-67 and 70 are directed to an immunogenic composition comprising an immunostimulant and a polypeptide comprising SEQ ID No. 176 or a portion thereof, or a polypeptide comprising an amino acid sequence having at least 75% or 90% identity to the sequence of SEQ ID No. 176, and the use of said immunogenic composition to induce an immune response in a patient.

Carney teaches that Ras oncogene has been found in wide array of premalignant and malignant cells and activated or mutated Ras proteins has been found in primary and metastatic tumors. Carney teaches generation of recombinant normal or mutated Ras proteins by using expression vector, production of polyclonal antibodies or monoclonal antibodies specific to Ras proteins, and detection, quantitation of Ras proteins in body fluids, tissues, or cells by using said antibodies (e.g. abstract, column 1, 2, 8-10). Carney further teaches using carrier protein and complete Freunds adjuvant to enhance immunogenicity of the peptide (e.g. column 15).

Carney does not teach the polypeptide sequence of SEQ ID No. 176 or a polypeptide that is at least 75% or 90% identical to SEQ ID No. 176.

Mueller-Pillasch teaches a human putative RNA binding protein KOC polypeptide sequence, SPTREMBL Accession No. O00425 (see computer printout mailed in preceding Official action), which is 100% identical to SEQ ID No. 176. Mueller-Pillasch also teaches that mRNA of the human KOC gene is highly overexpressed in pancreatic cancer cell lines and in pancreatic cancer tissue as compared to normal pancreas and chronic pancreatitis tissue (e.g. abstract).

It would have been obvious for one of ordinary skill at the time of the invention to substitute the Ras polypeptides with the human KOC polypeptide to produce polyclonal antibody or monoclonal antibody specific to said KOC polypeptide because they both are polypeptides and it was general knowledge to use polypeptide to immunize an animal, such as a rabbit, to produce antibody against said polypeptide.

One having ordinary skill at the time the invention was made would have been motivated to do so in order to produce antibody specific to the human KOC polypeptide more efficiently by using immunostimulant, such as adjuvant, as taught by Carney. Since the human KOC transcript is highly overexpressed in pancreatic cancer cell lines and in pancreatic cancer tissue as compared to normal pancreas and chronic pancreatitis tissue, one having ordinary skill would have been motivated to use the human KOC cDNA sequence to generate the human KOC polypeptide and use said KOC polypeptide to raise antibody specific to said KOC polypeptide in order to detect the expression level of KOC polypeptide in a biological sample or in pancreatic cancer tissues as compared to normal pancreatic tissues with reasonable expectation of success as taught by Carney and Mueller-Pillasch.

***Conclusion***

No claim is allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See M.E.P.. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Scott Priebe can be reached on (703) 308-7310. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Patsy Zimmerman, whose telephone number is (703) 305-2758.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER

Shin-Lin Chen, Ph.D.